REMARKS

Claims 1-54 are pending. Claims 1-15 and 43-54 are withdrawn. Claims 16-42 are under examination. Claims 16 and 20 have been amended.

Information Disclosure Statement

A copy of a reference referred to in the Information Disclosure Statement of January 10, 2005 was submitted to the Examiner with the Amendment of June 22, 2006 and has been entered into record.

Claim Objections

Claim 16 is objected to because of the following informalities: Step (k) of claim 16 recites "Dnasel" which should be replaced with "Dnase I". According to the Examiner's suggestion, step (k) of claim 16 as presently amended recites "Dnase I."

Claim Rejections Under 35 USC § 112

Claims 16 and 20-28 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the Applicants regard as the invention. Specifically, the Examiner alleges that in claim 16, the recitation "step (a)(i)" is unclear and lacks antecedent basis, and that in claim 20, the recitation "suitable for use" does not clearly define the encompassed subject matter.

Applicants traverse these grounds for rejection and submit that the application satisfies the requirements of §112. Nevertheless, without acquiescence in any rejection and solely for purposes of advancing prosecution, claim 16 as presently amended recites "step (i) of step (a)," according to the Examiner' suggestion, and claim 20 as amended herewith is directed in pertinent part to a composition for preparing an electrophoresis medium, and no longer recites the terms "suitable" and "use." Accordingly, Applicants submit that claims 16 and 20-28 are definite, in that they particularly point out and distinctly claim the subject matter which is regarded as the invention. In view of the present amendments, Applicants respectfully request withdrawal of the rejections under 35 U.S.C. §112, second paragraph.

Claim Rejections Under 35 U.S.C. § 102

Claims 17-23, 25, 27-38, 40 and 42 are rejected under 35 USC 102(b) as being anticipated by Cole (U.S. Patent No. 6,203,680). In particular, the PTO asserts that Cole prepares gellan gum according to the procedures described in Doner et al., and that Doner et al. teach purified gellan compositions having diminished levels of *phosphorus* contamination, alleging further that "the Cole composition indeed comprises gellan with significantly reduced levels of *nucleic acids*" where phosphorus is present in nucleic acids (Action at page 5, emphasis added).

Applicants traverse these grounds for rejection. The instant embodiments are directed in pertinent part to a gellan composition comprising gellan and either no nucleic acid or nucleic acid at a concentration of less than 10ppm based on the weight of the gellan. For reasons given herein, the cited documents describe, at best, a gellan composition having a nucleic acid concentration that is at least 100-fold greater than the maximum concentration permitted according to the present claims.

The PTO fails to establish a case of anticipation of the claimed subject matter over Cole because the cited publication fails to disclose each and every limitation of the instant claim. In particular, the gellan composition in Cole, as prepared according to Doner et al., is not a gellan composition that contains either no nucleic acid or nucleic acid at a concentration of less than 10 ppm based on the weight of the gellan.

Applicants submit that Cole and Doner et al. are silent with respect to quantifying the amount of *nucleic acid* that is present in the gellan compositions that are described in these documents. Contrary to the assertion found in the Action, the disclosure of Doner et al. fails to teach or suggest a gellan composition comprising nucleic acid at a concentration of less than 10 ppm based on the weight of the gellan. Doner et al. merely show that levels of *phosphorus* in their gellan preparations can be reduced, but such disclosure by Doner et al. cannot be regarded as in any way suggesting, whether expressly or inherently, a gellan composition having a *nucleic acid* concentration of less than 10 ppm. As such, Doner et al. and Cole both fail to demonstrate

gellan having *nucleic acid* levels that are sufficiently reduced according to the presently claimed embodiments.

Applicants submit that the PTO errs in its reliance on the inference that Cole teaches gellan having sufficiently diminished *nucleic acid* levels, based on disclosure by Doner et al. of gellan having diminished *phosphorus* levels. Furthermore, the PTO asserts incorrectly that from teachings in Doner et al. of gellan having reduced *phosphorus* levels (where phosphorus is known to be present in nucleic acids), the gellan compositions of Cole must contain a sufficiently reduced *nucleic acid* concentration. Specifically, and for reasons given below, even the decreased phosphorus level in the gellan of Doner et al. represents a nucleic acid concentration that is more than one hundred-fold higher than the maximum permissible nucleic acid concentration according to the present claims.

In particular, it is well known in the art that DNA contains about 8% phosphorus by weight (*see, e.g.,* Cavalieri et al., 1950 *J. Amer. Chem. Soc.* 72:4686, copy enclosed), *i.e.*, phosphorus accounts for slightly more than one twelfth of the dry weight of DNA. Therefore, when phosphorus is present as a component of a nucleic acid such as DNA (*e.g.*, contaminating DNA in a gellan preparation, as discovered and disclosed by the present application), the amount (by weight) of nucleic acid that is present is greater than twelve times the amount of phosphorus that is present. The gellan of Doner et al. as used by Cole, which as disclosed by Doner et al. (*e.g.*, at page 224, Table 1) contains *phosphorus* at 0.011% by weight, consequently contains more than twelve times as much *nucleic acid* by weight as phosphorus, *i.e.*, the gellan of Cole therefore contains at least 0.13% nucleic acid by weight. Accordingly, the gellan of Cole prepared by the method of Doner et al. likely contains *more than* 1,300 ppm nucleic acid based on the weight of the gellan, which is *well over one hundred times* the permissible maximum concentration of 10 ppm recited by the instant claims.

Even assuming, *arguendo*, that DNA contained 10% (instead of 8%) *phosphorus* by weight, a gellan composition containing *nucleic acid* at a concentration of less than 10ppm, as recited in the instant claims, would only contain *phosphorus* at a concentration of less than 1 ppm, or 0.0001%. As such, the gellan compositions according to the present claims contain over

one hundred-fold *less* phosphorus than the gellan disclosed in Cole and Doner et al., and so cannot be anticipated by either or both of these references.

Because neither Cole nor Doner et al. disclose a gellan composition containing either no nucleic acid or nucleic acid at a concentration of less than 10ppm based on the weight of the gellan, Applicants respectfully submit that the presently claimed subject matter can be distinguished readily over the cited documents. Reconsideration of the claims and withdrawal of the rejection under §102(b) are respectfully requested.

Claim Rejections Under 35 USC § 103

Claims 17-42 are rejected under 35 USC 103(a) as being unpatentable over Cole (U.S. Patent No. 6,203,680, " '680") in view of Nochumson et al. (U.S. Patent No. 5,143,646). In particular, the PTO asserts that Cole anticipates claims 17-23, 25, 27-38, 40, and 42, as discussed above, but concedes that Cole does not teach a gellan composition having an imidazole buffer. The Examiner alleges, however, that Nochumson et al. remedy the deficiencies in Cole by teaching gellan electrophoretic resolving gels and buffers, including an imidazole buffer, to assert that the skilled person would have found it obvious to combine the gellan composition of Cole with the electrophoresis buffers of Nochumson et al.

Claims 16-42 are rejected under 35 USC 103(a) as being unpatentable over Cole ('680) in view of Nochumson et al. and further in view of Cole et al. (1999 *Appl. Biochem. Biotechnol.* 82:57-76). More specifically, the PTO asserts that Cole et al. (1999) remedy any deficiencies in the assertion of obviousness over the combination of Cole ('680) and Nochumson et al., particularly with regard to treatment by Cole et al. of plasmid preparations with DNase I prior to electrophoresis of the plasmid preparations on a gellan gum gel.

Applicants respectfully traverse these grounds for rejection, for reasons given herein and also for reasons previously made of record. The present invention is directed in pertinent part to a gellan composition comprising gellan and either no nucleic acid or nucleic acid at a concentration of less than 10 ppm based on the weight of the gellan.

The PTO fails to set forth a *prima facie* case of obviousness under 35 USC §103(a). (*See In re Mayne*, 104 F.3d 133, 1341-43, 41 U.S.P.Q.2d 1451 (Fed. Cir. 1997) (PTO

has the burden of showing a *prima facie* case of obviousness.)). The PTO must show (1) that the cited reference(s) teaches or suggests all claim elements; (2) that the reference provides some teaching, suggestion, or motivation to combine or modify the teachings of the prior art to produce the claimed invention; and (3) that according to the teachings of the reference, a person having ordinary skill in the art will achieve the claimed invention with a reasonable expectation of success.

Cole ('680), Cole et al. (1999) and Nochumson, whether taken each alone or in any combination, fail to teach or suggest the presently claimed invention. Briefly, and as also discussed above, Cole ('680) fails to teach or suggest a composition comprising gellan and either no nucleic acid or nucleic acid at a concentration of less than 10 ppm based on the weight of the gellan, deficiencies which are not remedied by Nochumson or Cole et al. (1999). As such, the asserted disclosures of Nochumson regarding electrophoresis gels and buffers add nothing to teach or suggest a composition comprising gellan having a nucleic acid at a concentration of less than 10 ppm.

As noted above, nucleic acid at a concentration of less than 10 ppm represents over one hundred-fold *less* phosphorus than the most phosphorus-depleted gellan that is disclosed in Cole ('680) and Doner et al. The PTO thus fails to establish a case of obviousness where the cited prior art *in toto* is silent with regard to gellan having a nucleic acid concentration that is less than 10 ppm, and where the Office Action fails to point to any evidence in the prior art for a gellan composition having nucleic acid at a concentration of less than 10 ppm. Applicants therefore urge the Examiner to reconsider the Remarks accompanying Applicants' Amendment as submitted to the PTO on June 22, 2006, in light of the present Remarks, and reiterate that the disclosure of Nochumson et al. has no relevance to the instant claims where Nochumson et al. merely provide cumulative teachings of electrophoresis reagents but fail to suggest gellan having less than 10 ppm nucleic acid.

With regard to the assertion by the PTO of Cole ('680), Nochumson et al. and Cole et al. (1999), Applicants respectfully traverse and submit that the claimed product is readily distinguishable from any teaching or suggestion of the prior art. Contrary to the allegations

found in the Action, the presently claimed subject matter is readily distinguishable from, and is in no way suggested by, the cited publications.

Applicants agree with the Examiner that where claim 16 is a product-by-process claim, "determination of patentability is based on the product itself" (Action at page 7, citing *In re Thorpe*). Applicants note, however, that the claimed product is not the same as any prior art product, and is nowhere suggested by any combination of references from the prior art. For reasons given herein, the claimed product-by-process can be readily distinguished from the prior art such that the rejections under §103 should be withdrawn.

The claimed subject matter is directed in pertinent part to a gellan composition prepared by a method that comprises combining nucleic acid-contaminated gellan with DNase to provide a mixture that is maintained under conditions where the DNase degrades at least some of the nucleic acid to provide purified gellan. Applicants submit that as recited by the claim, the product can be readily distinguished from any product of the prior art. Specifically, the purified gellan which results from the method of claim 16(a) is not, and most certainly cannot be, the same as the gellan of Cole et al. (1999) or any other prior art product.

In particular, the claimed product-by-process is different because it lacks contaminating DNA that was present in the original gellan preparation, by virtue of such DNA having been degraded by the DNase. In marked contrast, and in stark rebuttal to the puzzling assertion found in the Action (page 8) that "it is irrelevant whether or not DNase serves to degrade any nucleic acid that may be present in the Cole composition", such contaminating DNA is present in the gellan of the prior art (such as the gellan of Cole et al. (1999)) because no degradation of the contaminating DNA is permitted to occur where in Cole et al. (1999) the DNase is inactivated prior to being contacted with the gellan. Thus, for instance, as disclosed in the specification (*e.g.*, at page 17, lines 4-19) the presently claimed product-by-process exhibits a dramatically reduced level of background staining when stained with a nucleic acid stain, compared to prior art gellan compositions which exhibit high background staining due to the presence of contaminating nucleic acid. The claimed product-by-process thereby differs from anything in the prior art.

As disclosed in the present specification, the prior art gellan compositions contain contaminating nucleic acid that is not present in the presently claimed gellan compositions. Even for the product-by-process of claim 16, the recited gellan composition is fundamentally different from any gellan composition taught or suggested by the prior art, because the prior art nowhere appreciated that gellan is contaminated with nucleic acids, much less suggested a gellan preparation in which the contaminating DNA has been degraded with DNase. Nor has the PTO pointed to any suggestion whatsoever in the art to prepare purified gellan compositions by degrading contaminating nucleic acid found therein. Where Cole et al. (1999) add EDTA to stop the DNase reaction prior to addition of the reaction mixture to gellan, the PTO errs in its assertion that the claimed subject matter is obvious over the teachings of Cole et al. (1999) in view of the other cited documents. The prior art in fact fails to provide any requisite motivation for combining DNase with gellan to degrade contaminating nucleic acid that is present in the gellan prior to the introduction of any DNA sample of interest into a gellan gel. As Applicants have also previously made of record, if anything, Cole et al. (1999) teach away from the claimed invention by failing to appreciate any benefit that might be obtained by permitting enzymatically active DNase to degrade DNA contaminating a gellan preparation.

Moreover, the Examiner apparently misapplies Cole et al. (1999) by asserting (Action page 9) that "the motivation discussed above to include plasmid preparations treated with DNase I *is not to degrade any nucleic acid in the Cole composition* (if any)" (emphasis and underscore added), and further, appears to misunderstand the application by continuing "[t]he fact that applicant has recognized another *advantage which would flow naturally from following the suggestion of the prior art* cannot be the basis for patentability. . ." (emphasis added)

On the contrary, Applicants submit that where the present application for the first time teaches the desirability of degrading nucleic acid that is present in a gellan preparation, the Examiner has apparently conceded that from the prior art, the skilled person would have lacked the motivation to treat gellan with DNase for purposes of obtaining a purified gellan composition. The DNase digestion disclosed in Cole et al. (1999) is a limited digestion that merely converts super-coiled DNA into the nicked or circular form, and in some cases, into truncated forms. The person having ordinary skill in the art would understand from Cole et al.

(1999) only that such use of DNase would reasonably and purposely be applied to a known, in-hand DNA *sample* for which such digested forms are sought. Applicants submit, however, that the skilled person would not have been motivated by the prior art to use DNase to degrade contaminating DNA in a gellan preparation even before the gellan is to be used as a separation medium for electrophoretic analysis of deliberately added nucleic acid samples.

In particular, and as noted above, none of the documents cited by the PTO recognize the problem of nucleic acid contaminants in gellan compositions. Support for this reading of Cole et al. (1999) is clearly provided by the fact that Cole et al. inactivate DNase with EDTA before the enzyme comes into contact with gellan. The Action thus appears to be beside the point by referring to a prior art composition which includes gellan, DNA and inactivated DNase. The claimed subject matter, by contrast, relates to a composition which comprises gellan having less than 10 ppm nucleic acid.

Further still, where the prior art as evidenced by Cole et al. (1999) adds EDTA to inactivate DNase before the enzyme contacts gellan, the Action errs in alleging that Applicants have disclosed an "advantage which would flow naturally from following the suggestion of the prior art." On the contrary, because of the very fact that the prior art fails to suggest or even remotely recognize any such "naturally flowing advantage" (*i.e.*, that DNase would beneficially reduce the amount of nucleic acid contaminating a gellan preparation), the presently claimed subject matter is not obvious. Nowhere does the prior art suggest, and nowhere has the PTO pointed to, any advantage to be gained by depleting a gellan preparation of nucleic acid (*e.g.*, using DNase) to obtain gellan having less than 10 ppm nucleic acid.

In summary, the PTO has failed to meet its burden of showing that the cited references teach or suggest all claim elements, nor has the PTO established that the references provide some teaching, suggestion, or motivation to combine or modify the teachings of the prior art to produce the claimed invention.

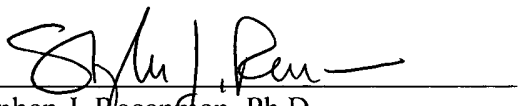
Applicants therefore respectfully submit that the PTO has not set forth a *prima facie* case of obviousness, and request withdrawal of the rejection under 35 U.S.C. §103(a). The Examiner is urged to contact the undersigned representative by telephone should any remaining issues require resolution.

The Director is authorized to charge any additional fees due by way of this Amendment, or credit any overpayment, to our Deposit Account No. 19-1090.

All of the claims remaining in the application are now clearly allowable. Favorable consideration and a Notice of Allowance are earnestly solicited.

Respectfully submitted,

SEED Intellectual Property Law Group PLLC



Stephen J. Rosenman, Ph.D.
Registration No. 43,058

SJR:rp

Enclosure:
Copy of Cavalieri et al., 1950 *J. Amer. Chem. Soc.* 72:4686

701 Fifth Avenue, Suite 6300
Seattle, Washington 98104-7092
Phone: (206) 622-4900
Fax: (206) 682-6031

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4. The systems phenylacetylene–methyl acrylate and styrene–diphenylacetylene copolymerize with a rate proportional to the square root of catalyst concentration. In the former case, abnormally high cross-termination is suggested.

PASSAIC, NEW JERSEY RECEIVED MARCH 17, 1950

[CONTRIBUTION FROM THE LABORATORIES OF THE SLOAN-KETTERING INSTITUTE FOR CANCER RESEARCH]

Studies on the Structure of Nucleic Acids. I. Interaction of Rosaniline with Desoxypentose Nucleic Acid[1]

BY LIEBE F. CAVALIERI AND ALICE ANGELOS

Introduction

The question of the structure of nucleic acids as they exist in solution, and in particular as they exist in living cells, has received a considerable amount of attention from various quarters. Organic and biochemical evidence has aided greatly in the elucidation of the nature of the covalent linkages, while physical chemical data, such as electrophoretic patterns, sedimentation rates, titration curves and X-ray studies have been more useful in the understanding of the secondary forces which are of importance in any detailed analysis of structure. Notwithstanding the abundance of data which confronts us, many questions regarding the fine structure remain unanswered. The more important problems deal with the sequence of the nitrogenous bases, the point of attachment in the sugar molecule of the various nucleotides and the extent and nature of the branching. The question as to whether nucleic acids are mixtures of polynucleotides rather than single entities is unanswered and has rendered the problem of structure still more nebulous.

The ability of nucleic acids to bind cationic dyes has been known for some time, but not until recently has any systematic and quantitative attempt been made to study this phenomenon. Thus, Michaelis[2] has observed and correlated spectrophotometric changes of basic dyes in the presence of nucleic acids. More recently the interaction of certain antimalarial drugs with pentose nucleic acid has been discussed.[3] Since the application of binding techniques to the study of protein structure[4,5] has resulted in a measure of success, we felt that a quantitative approach to the problem on hand would yield useful information which could be correlated with existing physico-chemical data.

Experimental

Materials.—The desoxypentose nucleic acid was a sample generously supplied by Dr. Aaron Bendich, prepared from calf thymus by a slight modification of the method of Hammarsten. The material was characterized as to purines, pyrimidines, and phosphorus content by Chargaff and co-workers.[6]

N, %	13.4	Guanine, %	7.4
P, %	8.0	Cytosine, %	4.7
Adenine, %	10.0	Thymine, %	8.4

The molecular weight of thymus DNA has been variously reported, but a value of 35,000 was used for calculations, based on the measurements of Jungner, Jungner and Allgen[7] and Hammarsten.[8] The acid- and alkali-treated samples of DNA were prepared according to Culland, Jordan and Taylor.[9] Analysis for alkali-treated sample: N, 14.1; P, 9.0; for acid-treated sample N, 13.3; P, 8.0.

The rosaniline was a commercial sample obtained from the Allied Chemical and Dye Corporation. After recrystallization from water, the nitrogen and chlorine analyses indicated 98 to 100% purity. In 0.05 *M* potassium phosphate buffer the extinction coefficient was 79,600 at *p*H 5.6 and 66,300 at *p*H 6.7 (5400 Å.). It was shown to obey Beer's law under the conditions of the study.

Anal. Calcd. $C_{20}H_{20}N_3Cl$: N, 12.48; Cl, 10.51. Found: N, 12.63; Cl, 10.31.

Method.—The binding of dye by DNA was determined by the method of equilibrium dialysis. Experiments were carried out at *p*H 5.6 and 6.7 in 0.05 *M* potassium phosphate buffer. DNA solutions varied from 0.05 to 0.2%. Five milliliters of DNA solution in 0.05 *M* buffer contained in a Visking cellophane bag were immersed in 5 ml. of dye in 0.05 *M* buffer. A group (*ca.* 24) of test-tubes was placed in a shaking device overnight which was sufficient time for equilibrium to be attained. The optical density of the solution of free dye (outside the bag) was determined in a Beckman spectrophotometer, Model DU, at a wave length of 540 mμ and the concentration calculated. Results were reproducible to within about 3%. Experiments were carried out at 3 ± 0.5°, 27 ± 1° and 32 ± 1°. Concentrations of DNA and dye were chosen such that a large proportion of dye was bound with respect to free dye concentration. The amount of dye adsorbed by the cellophane casing at each equilibrium concentration was determined from separate runs and found to be about 20% of the free dye concentration at *p*H 6.7. At *p*H 5.6 the cellophane adsorption ranged from about 30% at low dye concentrations to 15% at high dye concentrations.

Results

The data on the binding of rosaniline hydrochloride by desoxypentose nucleic acid (DNA) are presented in Figs. 1 and 2 and Tables I and II. The figures in the fifth column of Table I represent free dye concentrations to which have been added the values for the casing adsorption. This facilitates the calculations of the figures in

(1) The authors wish to acknowledge the support of the National Cancer Institute of the United States Public Health Service, the James Foundation of New York, Inc., and the joint support of the Office of Naval Research and the Atomic Energy Commission, contract N6-ori-99.

(2) Michaelis, *Cold Spring Harbor Symposia on Quantitative Biology*, **XII**, 131 (1947).

(3) Irvin, Irvin and Parker, *Science*, **110**, 426 (1949).

(4) Karush and Sonenberg, THIS JOURNAL, **71**, 1369 (1949); Karush, *ibid.*, **72**, 2705 (1950).

(5) Klotz and Urquhart, *ibid.*, **71**, 847 (1949).

(6) Chargaff, Vischer, Doniger, Green and Misani, *J. Biol. Chem.*, **177**, 405 (1949).

(7) Jungner, Jungner and Allgen, *Nature*, **163**, 849 (1949).

(8) Hammarsten, *Acta Med. Scand. Supp.*, 196 (1947).

(9) Culland, Jordan and Taylor, *J. Chem. Soc.*, 1131 (1947).